

Please amend page 20, line 1 as follows:

**Claims What is claimed is:**

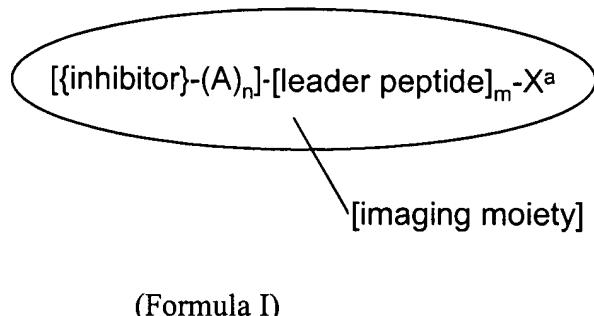
This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1. (Original) An imaging agent which comprises a synthetic caspase-3 inhibitor labelled with an imaging moiety, wherein the caspase-3 inhibitor has a  $K_i$  for caspase-3 of less than 2000 nM, and wherein following administration of said labelled caspase-3 inhibitor to the mammalian body *in vivo*, the imaging moiety can be detected either externally in a non-invasive manner or *via* use of detectors designed for use *in vivo*
2. (Cancel) The imaging agent of Claim 1, where the synthetic caspase-3 inhibitor has a  $K_i$  for caspase-3 of less than 500 nM.
3. (Currently amended) The imaging agent of ~~Claims 1 or 2~~Claim 1, where the synthetic caspase-3 inhibitor has a molecular weight of 150 to 3000 Daltons.
4. (Currently amended) The imaging agent of ~~Claims 1 to 3~~Claim 1, where the imaging moiety comprises:
  - (i) a radioactive metal ion;
  - (ii) a paramagnetic metal ion;
  - (iii) a gamma-emitting radioactive halogen;
  - (iv) a positron-emitting radioactive non-metal;
  - (v) a hyperpolarised NMR-active nucleus;
  - (vi) an optical dye suitable for *in vivo* imaging.
5. (Currently amended) The imaging agent of ~~claims 1 to 4~~Claim 1, which further comprises a 4 to 20-mer leader peptide sequence, wherein said leader peptide

facilitates cell membrane transport from the outside to the inside of a mammalian cell *in vivo*.

6. (Currently amended) The imaging agent of Claim 5 where the synthetic caspase-3 inhibitor conjugate is of Formula I:



where:

{inhibitor} is the a caspase-3 inhibitor with a Ki for caspase-3 of less than 2000 nM of claims 1 to 3;

[leader peptide] is as defined in Claim [4] 5 and is attached by either its' amine or carboxyl terminus;

-(A)<sub>n</sub>- is a linker group wherein each A is independently -CR<sub>2</sub>- , -CR=CR- , -C≡C- , -CR<sub>2</sub>CO<sub>2</sub>- , -CO<sub>2</sub>CR<sub>2</sub>- , -NRCO- , -CONR- , -NR(C=O)NR- , -NR(C=S)NR- , -SO<sub>2</sub>NR- , -NRSO<sub>2</sub>- , -CR<sub>2</sub>OCR<sub>2</sub>- , -CR<sub>2</sub>SCR<sub>2</sub>- , -CR<sub>2</sub>NRCR<sub>2</sub>- , a C<sub>4-8</sub> cycloheteroalkylene group, a C<sub>4-8</sub> cycloalkylene group, a C<sub>5-12</sub> arylene group, or a C<sub>3-12</sub> heteroarylene group, an amino acid or a monodisperse polyethyleneglycol (PEG) building block;

R is independently chosen from H, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> alkoxyalkyl or C<sub>1-4</sub> hydroxyalkyl;

n is an integer of value 0 to 10,

m is 0 or 1;

and X<sup>a</sup> is H, OH, Hal, NH<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkoxyalkyl, C<sub>1-4</sub> hydroxyalkyl or X<sup>a</sup> is the imaging moiety.

7. (Currently amended) The imaging agent of Claims 1 to 6Claim 1, where the radioactive metal ion is a gamma emitter or a positron emitter.

8. (Original) The imaging agent of Claim 7, where the radioactive metal ion is  $^{99m}\text{Tc}$ ,  $^{111}\text{In}$ ,  $^{64}\text{Cu}$ ,  $^{67}\text{Cu}$ ,  $^{67}\text{Ga}$  or  $^{68}\text{Ga}$ .

9. (Currently amended) The imaging agent of ~~Claims 1 to 6~~Claim 1, where the paramagnetic metal ion is Gd(III), Mn(II) or Fe(III).

10. (Currently amended) The imaging agent of ~~Claims 1 to 6~~Claim 1, where the gamma-emitting radioactive halogen is  $^{123}\text{I}$ .

11. (Currently amended) The imaging agent of ~~Claims 1 to 6~~Claim 1, where the positron-emitting radioactive non-metal is chosen from  $^{18}\text{F}$ ,  $^{11}\text{C}$ ,  $^{124}\text{I}$  or  $^{13}\text{N}$ .

12. (Currently amended) The imaging agent of ~~Claims 1 to 11~~Claim 1, where the synthetic caspase-3 inhibitor comprises one or more of the caspase-3 inhibitors defined in (i) to (ix):

(i) a tetrapeptide derivative of Formula III

$\text{Z}^1\text{-Asp-Xaa1-Xaa2-Asp-X}^1$  (III)

where  $\text{Z}^1$  is a metabolism inhibiting group attached to the N-terminus of the tetrapeptide;

Xaa1 and Xaa2 are independently any amino acid;

$\text{X}^1$  is an  $-\text{R}^1$  or  $-\text{CH}_2\text{OR}^2$  group attached to the carboxy terminus of the tetrapeptide;

where  $\text{R}^1$  is H,  $-\text{CH}_2\text{F}$ ,  $-\text{CH}_2\text{Cl}$ ,  $\text{C}_{1-5}$  alkyl,  $\text{C}_{1-5}$  alkoxy or  $-(\text{CH}_2)_q\text{Ar}^1$ , where q is an integer of value 1 to 6 and  $\text{Ar}^1$  is  $\text{C}_{6-12}$  aryl,  $\text{C}_{5-12}$  alkyl-aryl,  $\text{C}_{5-12}$  fluoro-substituted aryl, or  $\text{C}_{3-12}$  heteroaryl;

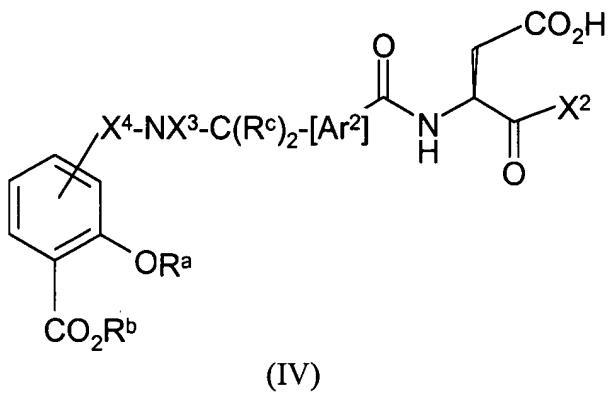
$\text{R}^2$  is  $\text{C}_{1-5}$  alkyl,  $\text{C}_{1-10}$  acyl or  $\text{Ar}^1$ ;

(ii) a quinazoline or anilinoquinazoline;

(iii) a 2-oxindole sulphonamide;

(iv) an oxoazepinoindoline;

(v) a compound of Formula IV



where  $X^2$  is H, C<sub>1-5</sub> alkyl or  $-(CH_2)_r-(S)_s-(CH_2)_tAr^3$ , where r and t are integers of value 0 to 6, s is 0 or 1 and  $Ar^3$  is C<sub>6-12</sub> aryl, C<sub>5-12</sub> alkyl-substituted aryl, C<sub>5-12</sub> halo-substituted aryl, or C<sub>3-12</sub> heteroaryl;

$Ar^2$  is C<sub>6-12</sub> aryl or C<sub>3-12</sub> heteroaryl;

$X^3$  is an  $R^b$  group;

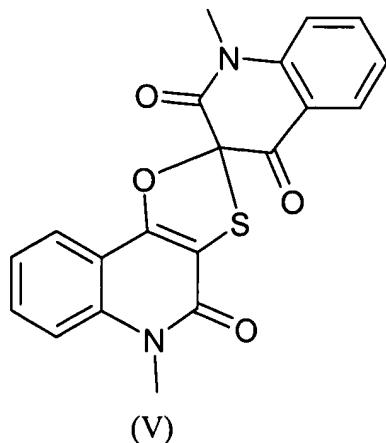
$X^4$  is  $-SO_2-$  or  $-CR_2-$

$R^a$  is H, C<sub>1-5</sub> alkyl or  $P^{GP}$  where  $P^{GP}$  is a protecting group;

$R^b$  is an  $R^a$  group or C<sub>1-5</sub> acyl;

each  $R^c$  is independently H or C<sub>1-5</sub> alkyl;

(vi) a compound of Formula V



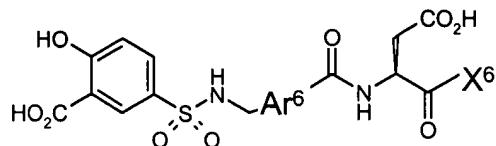
(vii) a pyrazinone;

(viii) a dipeptide of Formula VI:



where the  $-\text{CH}_2\text{SR}^1$  group is attached to the carboxy terminus of the dipeptides, and  $Z^1$  and  $R^1$  are as defined for Formula (III);

(ix) a salicylic acid sulphonamide of Formula XI:



Formula XI

Where  $Ar^6$  is a 5 or 6-membered  $C_{4-6}$  aryl or heteroaryl ring, and  $X6$  is H or  $-\text{CH}_2\text{SR}^2$ , where  $R2$  is as defined above.

13. (Original) The imaging agent of Claim 12, where the synthetic caspase-3 inhibitor comprises:

- (i) a tetrapeptide of Formula III; or
- (ii) a 2-oxindole sulphonamide; or
- (iii) a dipeptide of Formula VI.

14. (Currently amended) The imaging agent of ~~Claims 1 to 13~~Claim 1, where the synthetic caspase-3 inhibitor is selective for caspase-3 over caspase-1, by a factor of at least 50.

15. (Currently amended) The imaging agent of ~~Claims 13 or 14~~Claim 13, where the synthetic caspase-3 inhibitor comprises a tetrapeptide of Formula III or a dipeptide of Formula VI.

16. (Currently amended) A pharmaceutical composition which comprises the imaging agent of ~~claims 1 to 15~~Claim 1 together with a biocompatible carrier, in a form suitable for mammalian administration.

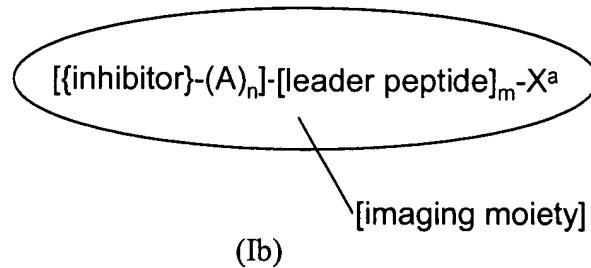
17. (Currently amended) A radiopharmaceutical composition which comprises the imaging agent of ~~claims 1 to 15~~ Claim 1 wherein the imaging moiety is radioactive, together with a biocompatible carrier, in a form suitable for mammalian administration.

18. (Original) The radiopharmaceutical composition of claim 17, where the imaging moiety comprises a positron-emitting radioactive non-metal or a gamma-emitting radioactive halogen.

19. (Original) The radiopharmaceutical composition of claim 17, where the imaging moiety comprises a radioactive metal ion.

20. (Currently amended) A conjugate of a synthetic caspase-3 inhibitor with a ligand, wherein the caspase-3 inhibitor has a  $K_i$  for caspase-3 of less than ~~2000~~ 500 nM, and wherein said ligand is capable of forming a metal complex with a radioactive or paramagnetic metal ion.

21. (Currently amended) The conjugate of Claim 20, of Formula Ib:



where  $A$ ,  $n$ ,  $m$  and  $X^a$  are as defined in Claim 6

$-(A)_n$  - is a linker group wherein each  $A$  is independently  $-\text{CR}_2-$ ,  $-\text{CR}=\text{CR}-$ ,  $-\text{C}\equiv\text{C}-$ ,  $-\text{CR}_2\text{CO}_2-$ ,  $-\text{CO}_2\text{CR}_2-$ ,  $-\text{NRCO}-$ ,  $-\text{CONR}-$ ,  $-\text{NR}(\text{C}=\text{O})\text{NR}-$ ,  $-\text{NR}(\text{C}=\text{S})\text{NR}-$ ,  $-\text{SO}_2\text{NR}-$ ,  $-\text{NRSO}_2-$ ,  $-\text{CR}_2\text{OCR}_2-$ ,  $-\text{CR}_2\text{SCR}_2-$ ,  $-\text{CR}_2\text{NRCR}_2-$ , a  $\text{C}_{4-8}$  cycloheteroalkylene group, a  $\text{C}_{4-8}$  cycloalkylene group, a  $\text{C}_{5-12}$  arylene group,

or a C<sub>3-12</sub> heteroarylene group, an amino acid or a monodisperse polyethyleneglycol (PEG) building block;

R is independently chosen from H, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> alkoxyalkyl or C<sub>1-4</sub> hydroxyalkyl;

n is an integer of value 0 to 10,

m is 0 or 1;

and X<sup>a</sup> is H, OH, Hal, NH<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkoxyalkyl, C<sub>1-4</sub> hydroxyalkyl or X<sup>a</sup> is the imaging moiety.

22. (Currently amended) The conjugate of Claims 20 or 21Claim 20, wherein the ligand is a chelating agent.
23. (Original) The conjugate of Claim 22, wherein the chelating agent has a diaminedioxime, N<sub>2</sub>S<sub>2</sub>, or N<sub>3</sub>S donor set.
24. (Currently amended) A kit for the preparation of the radiopharmaceutical composition of Claim 19, which comprises the conjugate of a synthetic caspase-3 inhibitor with a ligand, wherein the caspase-3 inhibitor has a K<sub>i</sub> for caspase-3 of less than 500 nM, and wherein said ligand is capable of forming a metal complex with a radioactive or paramagnetic metal ion.Claims 20 to 23.
25. (Original) The kit of Claim 24, where the radioactive metal ion is <sup>99m</sup>Tc, and the kit further comprises a biocompatible reductant.
26. (Currently amended) A kit for the preparation of the radiopharmaceutical composition of Claim 18, which comprises a precursor, said precursor being a non-radioactive derivative of the a caspase-3 inhibitor of claims 1 to 15, wherein the caspase-3 inhibitor has a K<sub>i</sub> for caspase-3 of less than 2000 nM, wherein said non-radioactive derivative is capable of reaction with a source of the positron-emitting radioactive non-metal or gamma-emitting radioactive halogen to give the desired radiopharmaceutical.

27. (Original) The kit of claim 26 where the precursor is in sterile, apyrogenic form.

28. (Currently amended) The kit of ~~Claims 26 or 27~~Claim 26, where the source of the positron-emitting radioactive non-metal or gamma-emitting radioactive halogen is chosen from:

- (i) a halide ion or  $F^-$  or  $I^-$ ; or
- (ii) b an alkylating agent chosen from an alkyl or fluoroalkyl halide, tosylate, triflate or mesylate;

29. (Currently amended) The kit of ~~Claims 26 to 28~~Claim 26, where the non-radioactive derivative is chosen from:

- (i) a an organometallic derivative such as a trialkylstannane or a trialkylsilane;
- (ii) b a derivative containing an alkyl halide, alkyl tosylate or alkyl mesylate for nucleophilic substitution;
- (iii) c a derivative containing an aromatic ring activated towards nucleophilic or electrophilic substitution;
- (iv) d a derivative containing a functional group which undergoes facile alkylation;
- (v) e a derivative which alkylates thiol-containing compounds to give a thioether-containing product.

30. (Currently amended) The kit of ~~claims 26 to 29~~claim 26, where the precursor is bound to a solid phase.

31. (Currently amended) Use of the imaging agent of ~~claims 1 to 15~~Claim 1 in a method of diagnosis of a caspase-3 implicated disease state of the mammalian body, wherein said mammal is previously administered with the pharmaceutical composition which comprises the imaging agent of Claim 1 together with a biocompatible carrier, in a form suitable for mammalian administration ~~of claim 16~~,

or the radiopharmaceutical composition which comprises the imaging agent of Claim 1 wherein the imaging moiety is radioactive, together with a biocompatible carrier, in a form suitable for mammalian administration of claims 17 to 19.